REMARKS

Claims 1-11 and 34-53 were previously canceled without prejudice to the filing of continuation and divisional applications. Claims 58 and 61 are canceled. No new matter is added in the amendment. Claims 12-33 and 54-57, and 59-60 are pending.

35 USC §112 Rejection

§112 first paragraph

The Examiner rejected claims 58 and 61 under §112 first paragraph as failing to comply with the written description requirement in that the specification does not support 1) " polymer is solid below the process temperature" as claimed in claim 58, 2) and "polyurethane polymer is a carrier polymer" as claimed in claim 61. Applicants respectfully traverse these rejections.

First, in Example 1 we clearly give an example of starting from GRANULES of polyurethane for the melt blending process, i.e., the granules were to be heated and blended. Applicants submit that granules of polyurethane are solid before the heating process. Any person skilled in the art will know the polyurethane granules mentioned in the Example were solid.

Second, Applicants wish to direct the Examiner's attention to page 2, lines 4 to 20 and page 9, lines 8-15 of the specification. In these sections, we describe the "drug in adhesive" in which drug is directly formulated into the adhesive and multilaminates, in which drug, enhancer and "polymer carrier", and solvent are cast on a substrate; whereas in melt-blending polyurethane drug and excipients are mixed into polyurethane (the polymer). Anybody skilled in the art will know that polyurethane is the carrier of the drug in melt-blending, just like polymer in multilaminate with solvent casting the polymer is the carrier.

Nevertheless, to speed up the grant of the claims, Applicant's has canceled claims 58 and 61 without prejudice.

Withdrawal of the rejection is respectfully requested.

35 USC §102 Rejection

The Examiner rejected claims 12, 13, 15-20, 22, 23, and 54 under 35 USC 102 as being anticipated by US4638043 ('043 Szycher). Applicants respectfully traverse the rejection. The Examiner asserted that "043 discloses a drug containing polyurethane layer and that the polyurethane has process temperature of less than 150°C. The Examiner asserts that the process temperature of polyurethane is inherent and that mixing the drug in the polyurethane layer before or after the curing is directed to method of product and does not impart patentability to the claims directed to product. The Examiner asserted that the end product is not materially different from the product of the prior art and that the reference (Szycher) disclosed the polyurethane made from the same elements as instantly claimed. Applicants respectfully traverse the rejection.

Szycher described only about UNCURED material as far as mixing or blending is concerned. He never mentioned that the cured material can be mixed or blended, regardless of temperature. He never mentioned that the polyurethane layer is liquid at room temperature, only that the precured oligomeric material is liquid (which before curing is not suitable for a matrix layer in the device because as a liquid it would flow). It is submitted that Szycher mixed PRECURED oligomeric liquid at room temperature (see column 2, lines 42-47) to be polymerized by curing, not the polymerized polymer. The liquid PRECURED polymeric liquid is not yet cured and therefore is not polyurethane. Szycher stated clearly that the drug dispensing member is comprised of "a polyurethane formed from an oligomer which is cured by actinic radiation....", the drug is incorporated in the material before the material is cured (Column 4, lines 10-14). The polyurethane is ***formed from an oligomer by curing***. Curing changes the thermal and mechanical property of a material, because of cross-linking formed in the curing reaction.

Szycher never mentioned melt blending. In fact, the word "melt" never appeared in the patent. Further, the only times Szycher talked about heat were on curing or that drugs were heat labile. Nothing was ever said about melting. Szycher '043 has nothing to do with melt blending polymer and drug.

In the presently claimed invention, the polyurethane polymer can be directly ***melt blended*** with the at least one drug at less than about 150 °C without an organic solvent. The polyurethane must be able to be processed by melt-blending. Obviously, as those skilled in the

art know, melt-blending involves melting to form a melt and blending a drug in the melt. On pages 3-4 we mentioned hot melt adhesive, process temperature and polyurethane. It is clear that to those skilled in the art that melt-mixing polyurethane with a drug involves melting the polyurethane and mixing in the drug (as we do in our Example 1). Such melt-blending usually is done with an extruder or some kind of a blender or mixer with a heater. There is no indication that the material described by Szycher can be processed in melt-blending.

The precured liquid material cannot be melt-blended, since it being already a liquid cannot be processed by melting. Just because something can be mixed in room temperature does not mean it can be melt-blended. By analogy, concrete mix before setting can be mixed in room temperature. That does not mean the concrete mix can be melt-blended. Second, there is no indication that after curing or cross-linking the cured polymers can be melt-blended at all. UV curing is an irreversible chemical reaction. Once cured, the material cannot be uncured. Thus, there is no indication that the polyurethane in the UV-cured material can be melt-blended anymore, much less be processed at a temperature of less than about 150 °C without an organic solvent. Again taking the analogy of concrete mixing, after concrete is set, it cannot be unset to be processed by melting and mixing. Where is the evidence that the cured polymer of Szycher can be melt-blended with drug?

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently as described, in a single reference. Verdegaal Bros. v Union Oil., 814 F2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir.), cert. denied, 484 U.S. 827 (1987). It is submitted that the Examiner has failed to show that all elements in the claims are found in the referenced Szycher patent.

The Examiner asserted that instant end product is not materially different from the product of the prior art. In contrast, it is submitted that our end product is different from the end product of Szycher. In certain claims, the transdermal drug delivery device has a drug reservoir comprising a melt-blended mixture of at least one drug and a polymer consisting of polyurethane polymer, in which the polyurethane polymer has a process temperature of less than about 150 °C, wherein the polymer can be directly melt blended with the at least one drug at less than about 150 °C without an organic solvent to result in the drug reservoir. Thus, in the ***end product***, the mixture includes a polyurethane that has a process temperature of less than about 150 °C, at which melt

blending can be done. Applicants respectfully ask the Examiner for the showing of any evidence that the Szycher end product has polyurethane that has such property. What is the melt blending process property of the ***cured*** polyurethane of the Szycher end product? There is no indication in Sxycher '043 that it is less than about 150 °C.

The Examiner asserted that curing is directed to method and does not impact patentability to claims directed product. Applicants respectfully disagree. Whether something is cured or not has great impact on the property of a device and thus impact patentability. For analogy, doesn't the claim "a tire made of uncured rubber" have patentability over references that all talk about tires made of cured rubber? Further, it is submitted that it is not our invention that requires curing, but rather it is the reference that does. By requiring curing, the referenced material has property vastly different from material that can be melt blended, and therefore cannot be used for anticipating the present invention.

The Examiner asserted that "the burden is on Applicants to show that blending the polymer with the drug after curing the polymer will provide a product materially different from [the] blending the polymer with drug before curing." This is like an examiner saying that the burden is on the applicant to show that a tire made by blending rubber with excipients without vulcanization is different from a tire made by blending excipients after vulcanization. The polymer after curing may not be blendable at all. We submit that it should be the Examiner's burden to show that the cured polymer is melt blendable and blending the polymer with the drug after curing the polymer will provide a product materially the same as melt-blending the polymer with drug without requiring curing.

The Examiner asserted Szycher on col 6, lines 20-23 "disclosed that the materials used to make the drug containing layers is the same as the materials used to make the substrate but without the drug" and that "therefore, TECOFLEX can be used for both the drug containing layer and the substrate." Applicants disagree.

The Examiner's characterization of the cited section is less than accurate and the logic is flawed. First, Szycher DID NOT "disclosed that the materials used to make the drug containing layers is the same as the materials used to make the substrate but without the drug". Rather, Szycher merely said that "the polyurethane formed in the drug release system" is also suitable

for the substrate layer. Szycher in the sections just before to the cited col 6, lines 20-23 was actually describing the making of the substrate l2. Then on col 6, line 17-20 Szycher said, "Also suitable for use is the polyurethane formed in the drug release system described above and set forth in U.S. Pat. No. 4,483,759 to Michael Axycher et al." Thus, clearly, Szycher did NOT disclose "the materials used to make the drug containing layers is the same as the materials used to make the substrate but without the drug" but rather that the material of the drug layer can be used for the substrate. This is a critical difference. A can be used for B does not mean B can be used for A and definitely does not mean A is the same as B. For analogy, a polished stainless steel reactor tank for making drugs can have painted carbon steel supporting legs. Somebody may teach that the polished stainless steel used for the reactor tank can also be used for making the supporting legs. It is a far cry from saying that he teaches the reactor tank is "made of the same material as" the supporting legs. Nobody in his right mind will think of using painted carbon steel for a tank reactor for making drugs. The requirement for reactor tank material is more restrictive than the requirement for material for supporting legs. The reactor tank material may be used for making support legs, but the reverse is not true. Likewise, the requirement for the material for the drug containing layer is much more restrictive than the requirement for the substrate. The polymer for the drug-containing layer being applicable for making the substrate does not mean the substrate material can be used for the drug-containing layer. Thus, Szycher did not teach that TECOFLEX (which is usable as substrate) can be used for the drug-containing layer at all.

Withdrawal of the rejection is respectfully requested.

35 USC §103 Rejection

The Examiner rejected claims 12-20, 22, 33, 54 and 58-61under 35 USC 103 as being unpatentable over US4638043 ('043,Szycher). Applicants respectfully traverse the rejection.

The Examiner asserted that "043 discloses a transdermal drug releasing patch that comprises support layer (i.e., backing layer), polymer layer of polyurethane containin a drug and a pressure sensitive adhesive layer and that the drug is contained in an amount of 1-10% in the polyurethane layer and includes analgesic. The Examiner further asserted that the polyurethane comprises reaction products of dicyclohexyl methane diisocyanate, polytetramethylene ether

polyol and 1,4-butane diol. Although the Examiner admitted that '043 does not explicitly teach that the process temperature and the modulus of the polyurethane polymer, she asserted that process temperature and the modulus of the polyurethane polymer disclosed by US'043 are expected to be the same as what is claimed in the instant application because the reference teaches the same polymer formed from the same polymer reaction that is liquid at room temperature and that it would be obvious to provide "polyurethane polymer layer containing a drug wherein the polyurethane layer is liquid at room temperature" and "adjust the temperatue to the required to melt the drug into the liquid polyurethane polymer according to specific drug used without the use of any solvents, motivated by the teaching of US '043...."

Applicants have shown above that melt-blending has never been suggested by US '043. Applicants further submit that it is not obvious from US'043 that a drug reservoir can be formed as a melt-blended mixture of a drug and a polymer consisting of polyurethane polymer, wherein the polymer can be directly melt blended with the at least one drug at less than about 150 °C without an organic solvent at all. As those skilled in the art will know, melt blending a polymer with a drug to form a transdermal patch reservoir involves melting the polymer and blending with the drug (e.g., as described in instant application about hot melt adhesive and in Example 1 in which granules of polyurethane is heated and melt-blended with drug; and as described in US6010715 in which matrix polymer is melted and blended with drug). Szycher never mentioned melting at all in the whole patent. It is clear that the oligomer in Szhcher '043 before curing is liquid and cannot be melted. The Examiner asserted that one would just adjust the temperature to that required to melt the drug into the liquid polyurethane polymer. Szycher simply never mentioned melting. Nothing was ever melted in Szycher '043. How then can Szycher give any motivation to melt-blending a polymer with a drug? Although a prior art device may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so. 916 F.2d 1260. 23 USPQ2d 1780 (Fed. Cir. 1992). How can there be any suggestion of melt blending if no melting is mentioned?

Regarding dicyclohexyl methane diisocyanate, polytetramethylene ether polyol and 1,4-butane diol, it is noted that these are mentioned in col 5, lines 39-43, which is the description on material for the substrate, not the drug containing material. Again, the Examiner is trying to use

material used in unrelated features for obviousness rejection. No one skilled in the art will use a material suggested for a substrate for use to contain drug in the drug releasing member.

The Examiner repeated the assertion that the reference '043 "suggested that both drug containing layer and the substrate layer can be made from the same polyurethane (col 6, lines 20-23). Again, this is based on the flawed logic that if the material of A can be used for B, then the material for B can be used for making A. Szycher only suggested that the material for making the drug releasing member can be used for making the substrate, but said nothing about the reverse.

Withdrawal of the rejection is respectfully requested.

The Examiner rejected claims 12-33, 54-61 under 35 USC 103 as being unpatentable over US4638043 in view of US5273757('757 Jaeger) or vise versa. Applicants respectfully traverse the rejection.

The irrelevance of US4638043 has been discussed above. Jaeger does not cure the shortcomings of '043. The Examiner asserted that specific drugs, permeation enhancers and acrylate adhesive do not impart patentability to the claims. However, different drugs and ingredients affect the temperature tolerance as well as the physical property of the drug-containing layer. Further, an important difference about '757 is that it teaches that the "pressure sensitive adhesive can contain only up to 10 to 50% by weight of polyurethane" (see column 6, lines 12-13). There are a lot of other material in the adhesive, such as 10-80% hydrogenated alcohol, 10-80% hydrocarbon resin, 1 to 40% of esters of vegetable fatty acids, and possible additionally up to 5% antiagers, and up to 70% fillers. Esters of vegetable fatty acids, hydrogenated alcohol, and hydrocarbon resin have plasticizer functions. It is a scientific fact that "plasticizers are able to decrease the glass transition temperature and the melt viscosity of a polymer.... With the addition of a plasticizer, a hot melt process can be conducted with lower temperature and with less torque." (quoted from Pharmaceutical Coating Bulletin 102-6, Morflex Inc. 2004. Said reference is quoted for scientific facts, not for prior art purpose). See also statement in US 5662923 (Roreger), col 3, lines 1-2 about pressure sensitive hot melt adhesive: "The softening temperature is reduced by so called plasticizers...." With a large amount of such non-polyurethane plasticizers in the Jaeger adhesive, the thermal property of the adhesive is very different from that of the polyurethane ingredient. There is no indication what the melt-blending

processing temperature of the polyurethane in the adhesive is. Jaeger only stated that the pressure sensitive adhesive has a processing temperature of 40 – 80 °C (see e.g., column 2 lines 50-51). But Jaeger did not say that the polyurethane has a processing temperature of 40 – 80 °C. There is a difference between the adhesive and its polyurethane ingredient, they are not one and the same. There is no indication that the polyurethane used by Jaeger has a processing temperature of 40 – 80 °C. Obviousness requires a reasonable expectation of success. See, In re O'Farrell 853 F.2d 894 903-4, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Even if one were assumed to want to try, there is not expectation of success that polyurethane without a large amount of plasticizer can be processed at that temperature range. Thus, even if assuming one would want the advantages of lower temperature processing and fentanyl and enhancers, one would not glean from Jaeger of melt mixing polyurethance that the polyurethane itself has a low melt-blending processing temperature.

Thus, it is not obvious at all that the polyurethane with processing temperature of less than 150°C is present in the adhesive in Jaeger.

The Examiner repeated the assertion in the rejection on '043 above that the process temperature is directed to the method of making and not a product. Again, Applicants submit the process temperature is a property of the device and thus is relevant for the patentability of the device.

Withdrawal of the rejection is respectfully requested.

The Examiner rejected claims 21, 28, 29, and 32 under 35 USC 103 as being unpatentable over US4638043 in view of US5273757('757 Jaeger) and further in view of US6139866 ('866 Chono). Applicants respectfully traverse the rejection.

The irrelevance of US4638043 and US5273757 have been discussed above. Chono did not cure the shortcomings of '043 and '757. The Examiner asserted that Chono disclosed formulations comprising fentanyl, acrylate adhesive, and permeation enhancers such as glycerol monolaurate and thus a skilled person would be motivated to use glycerol monolaurate and use acrylate as skin contact adhesive. However, it is noted that Chono did not mention polyurethane for the drug layer at all. Where Chono mentioned polyurethane, he only refered to the backing layer (column 5, line 43-44). Thus, Chono never intended polyurethane to be used in the drug

layer, but only for the backing layer. Further, the adhesive/drug mixing was apparently done with solvent (column 5, lines 24-35). Thus, although the Chono patent discloses fentanyl and certain permeation enhancers, it certainly is irrelevant for melt-blending with drug at a low temperature using a polyurethane polymer that can be processed at or below 150 °C. Chono apparently thought of polyurethane as unsuitable for holding the drug and enhancers. Of course, an enhancer that works for one adhesive may not work for another adhesive. Even if one were assumed to want to combine Chono with the other references, one would only use enhancers for non-polyurethane reservoir and only use polyurethane for the backing.

The Examiner asserted that there is reasonable expectation of having a transdermal melt blend matrix comprising polyurethane, fentanyl and glycerol monolaurate and acrylate adhesive skin contact layer. Applicants submit that Chono, never having mentioned polyurethane as usable for containing the drug, would provide no expectation of success at all.

Claims 21, 28, and 30 are rejected under 35 USC 103 (a) as being unpatentable over US4638043 in view of US5273757('757 Jaeger) and further in view of US5066648 ('648 Alexander). Applicants respectfully traverse the rejection.

The irrelevance of US4638043 and US5273757 has been discussed above. Alexander does not cure the shortcomings of '043 and '757. The Examiner asserted that Alexander teaches pyroglutamic acid esters as permeation enhancers for analgesics and sedatives, and therefore one skilled in the art will be led to deliver fentanyl with the enhancers in our claimed invention. However, surely the Examiner is not saying that all analgesics and sedatives can be delivered with the aid of a particular permeation enhancer and that just because a permeation enhancer works with one analgesic it would work with all other analgesics. Anybody skilled in the art knows that permeation enhancers do not function the same way for different drugs in different matrixes. An enhancer that works for drug A may not work for drug B in the same polymer. Further, an enhancer that works in a polymeric matrix may not work in another polymeric matrix. Alexander does not mention fentanyl, and does not mention polyurethane as the drug layer carrier polymer. Furthermore, Alexander has nothing to do with melt-blending. Even if it is assumed that one would combine the references there is no expectation of success that fentanyl can be effectively delivered in a polyurethane melt blended mix. Thus, a person skilled in the art

will not look to Alexander for suggestions on melt-blending of fentanyl in polyurethane at all. Even if one is assumed for argument's sake to look for guidance at Alexander, there is no expectation of success.

Withdrawal of the rejection is respectfully requested.

The Examiner rejected claims 32 under 35 USC 103(a) as being unpatentable over US4638043 in view of US5273757('757 Jaeger) and further in view of US5599648 (however, Applicants think the Examiner was actually referring to US5599289 ('289 Castellana)) instead. Applicants respectfully traverse the rejection.

The irrelevance of US4638043 and US5273757 has been discussed above. Castellana does not cure the shortcomings of '043 and '757. The Examiner asserted that Castellana teaches wound dressing comprising skin contact acrylate adhesive layer and therefore one would make the presently claimed invention. However, There is no description by Castellana that another polymer is used as an adhesive on a drug reservoir having a different polymer, much less having an acrylate adhesive on a polyurethane reservoir. Thus, the use of acrylate adhesive by Castellana is entirely different from what is claimed in claim 32. A polymer to be used as a drug reservoir by itself may not be suitable for use to be placed on another reservoir drug layer that has a different polymer. In this claimed structure, the drug has to pass from the polyurethane reservoir into the acrylate adhesive before reaching the skin. Castellana does not teach that and there is no expectation of success from Castellana even if one were assumed to want to try. For example, depending on the layers, the solubility of the skin contacting adhesive for the drug may be so high that the concentration of the drug in that skin contacting adhesive may not be high enough to produce an effective flux. Without using the present disclosure as a guide, one would not have any expectation of success. However, "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596 (Fed.Cir.1988) *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596 (Fed.Cir.1988) (*In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed.Cir.1999)).

And Castellana has no mention of fentanyl. Thus, who knows what fentanyl will do in the two adhesive layers. An adhesive that works for one drug may not be effective for transdermal delivery for another drug.

Furthermore, there is no mention of melt mixing temperature and thus Castellana is far removed from the presently claimed invention. Even less predictable is the combination of two different adhesive layers through which fentanyl has to migrate. Thus, even if with the assumption that some one would want to combine the references as asserted by the Examination, there is no expectation of success.

Withdrawal of the rejections is respectfully requested.

CONCLUSION

Applicants submit the pending claims are novel and nonobvious over prior art and comply with the requirements of 35 USC 112. The examination and passage to allowance of the pending claims are respectfully requested. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (650) 564-7054 to clarify any unresolved issues raised by this response.

The Commissioner is hereby authorized to charge any additional fees associated with this paper or during the pendency of this application, or credit any overpayment, to Deposit Account No. 10-0750.

Respectfully submitted,

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